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| EXAMINER | |
|---|---|
| SWOPE, SHERIDAN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/553,869 | LORENTSEN ET AL. | |
| | Examiner | Art Unit | |
| | Sheridan L. Swope | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05-JUL-07, 24-OCT-07, 13-NOV-07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *12 and 18-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-17* is/are rejected.

7)☒ Claim(s) *1-11 and 13-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0206;0806*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's election, without traverse, of Invention I, as well as human granzyme B in their response of July 5, 2007 is acknowledged. Applicant's further election of the recognition site IEXD in their response of October 24, 2007 is acknowledged. Applicant's further election of the recognition site IEAD, by telephonic interview with Applicants' representative, Stan Aksman, on November 13, 2007, is acknowledged. The elected invention is directed to a method of cleaving a fusion protein using a human granzyme B enzyme, wherein the fusion protein comprises the cleavage motif IEAD. Claims 1-39 are pending. Claims 12 and 18-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1-11 and 13-17 are hereby examined.

### *Priority*

The priority date granted for the instant invention is April 23, 2003, the filing date for US 60/464,663 and Denmark PA2003-00616, both of which disclosed the elected invention.

### *Drawings-Objections*

Figure 2 is objected to for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO: ). The sequence rules embrace all nucleotide sequences with ten or more bases and all amino acid sequences with four or more amino acids. Said sequences must be disclosed in a sequence listing and identified by a specific SEQ ID NO: (MPEP 2421.02). 37 CFR 1.821(d) requires the use of the assigned sequence identifier number in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims of an application. Applicant is

required to check the disclosure completely and to make corrections to identify all of the sequences disclosed therein by sequence identifier numbers.

***Specification-Objections***

The specification is objected to for containing hyperlinks. USPTO policy does not permit the USPTO, i.e, via an issued patent, to refer to any commercial sites, since the USPTO exercises no control over the organization, views or accuracy of the information contained on these outside sites. Hyperlinks and other forms of browser-executable code, especially commercial site URLs, are not to be included in a patent application. (MPEP 608.01) The specification should be carefully checked and all URLs removed.

The specification is objected to for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO: ). The sequence rules embrace all nucleotide sequences with ten or more bases and all amino acid sequences with four or more amino acids. Said sequences must be disclosed in a sequence listing and identified by a specific SEQ ID NO: (MPEP 2421.02). 37 CFR 1.821(d) requires the use of the assigned sequence identifier number in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims of an application. Applicant is required to check the disclosure completely and to make corrections to identify all of the sequences disclosed therein by sequence identifier numbers.

The specification is objected to for disclosing conflicting information regarding the structure of GrB-H6. In Example 1, pg 32, parg 1, the specification states that "a sequence encoding activated human Granzyme B (E.C. 3.4.21.79), i.e. from Ile21 (Ile16 in chymotrypsinogen numbering) to Tyr246, was cloned into a pT7 cloning vector containing a

hexa-His tag (H6) C-terminally", wherein the "recognition sequence IEGR was thereby placed just N-terminally to Ile21 in Granzyme B". The same paragraph also states the sequence of said construct is, "referred to as pro-IEGR-GrB-H6 and is shown in SEQ ID NO: 1". However, SEQ ID NO: 1 fails to disclose an Ile21 (or Ile16 in chymotrypsinogen numbering) or a Tyr246 (or Tyr241 by chymotrypsinogen numbering). Moreover, the residue just prior to the H6 tail is not a tyrosine. Thus, the specification is objected to for disclosing conflicting information regarding the structure of pro-IEGR-GrB-H6, and thus, the sequence of GrB-H6. Applicants are required to check the disclosure completely to make sure the textural description of all constructs is consistent throughout and agrees with the sequence listing.

***Claims-Objections***

The claim set is objected to for not beginning with a sentence of which the claims are an object e.g., "We claim" or "The claims are".

Claims 1-11 and 13-17 are objected to for reciting non-elected subject matter.

Claims 2-5 are objected to for disclosing sequences that are not identified by a sequence identifier number (SEQ ID NO: ). The sequence rules embrace all nucleotide sequences with ten or more bases and all amino acid sequences with four or more amino acids. Said sequences must be disclosed in a sequence listing and identified by a specific SEQ ID NO: (MPEP 2421.02). 37 CFR 1.821(d) requires the use of the assigned sequence identifier number in all instances where the description or claims of a patent application discuss sequences, regardless of whether a given sequence is also embedded in the text of the description or claims of an application. Applicant is required to check the disclosure completely and to make corrections to identify all of the sequences disclosed therein by sequence identifier numbers.

***Claim Rejections - 35 USC § 112-Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 13-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claim 5 is rendered indefinite by failing to define P1', P2' or P3'. The skilled artisan would not know the metes and bounds of the recited invention. For purposes of examination, it is assumed that P1', P2', and P3' are defined as any amino acid.

Claim 17 is rendered indefinite for failing to further limit the claim from which it depends. For purposes of examination, it is assumed that Claim 17 is meant to be dependent from Claim 16.

Claims 1-11 and 13-17 are rendered indefinite by improper antecedent usage, as follows.

In each of Claims 2-11 and 13-17, the phrase "A method according to claim..." should be corrected to "The method according to claim...".

For Claim 1(c), the phrase "a polypeptide of interest" should be corrected to "the polypeptide of interest".

Examiner's note: The specification states:
"'Granzyme B protease' (also referred to herein as GrB) includes enzymes which are or may be classified under the Enzyme Commission number EC 3.4.21.79 in Enzyme nomenclature database, Release 34, February 2004."
The genus EC 3.4.21.79 is defined as a peptidase of the S1 family with preferential cleavage of -Asp-|-Xaa- >> -Asn-|-Xaa- > -Met-|-Xaa-, -Ser-|-Xaa- (NiceZyme View of ENZYME: EC 3.4.21.79). Therefore, the phrase Granzyme B protease, as used in the instant application, is taken to mean any protease of the S1 family with preferential cleavage of -Asp-|-Xaa- >> -Asn-|-Xaa- > -Met-|-Xaa-, -Ser-|-Xaa-, wherein the protease has any structure.

***Claim Rejections - 35 USC § 112-First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Enablement**

Claims 1-11 and 13-17 are rejected under 35 U.S.C. 112, first paragraph. Examples 6 and 8 of the specification disclose use of enzymes named GrB-H6 and GrB-H6-C228F for the cleavage of a variety of fusion proteins. However, as explained above for objection to the specification, the disclosure fails to clearly teach the structure/sequence of said enzymes. Therefore, the specification fails to enable the skilled artisan to make and use said enzymes in the recited method. Moreover, the specification does not reasonably provide enablement for a method to cleave a fusion protein comprising any granzyme B cleavage motif using any granzyme B enzyme having any structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or

absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 1-11 and 13-17 are so broad as to encompass a method for cleaving a fusion protein comprising any granzyme B cleavage motif using any granzyme B enzyme having any structure. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired cleavage activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In this case, the disclosure fails to clearly teach the structure of any enzyme having the desired activity.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims. Furthermore, the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable (Galye et al, 1993; Whisstock et al, 2003). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1-11 and 13-17, which encompasses all methods for cleaving a fusion protein comprising any granzyme B cleavage motif using any granzyme B enzyme having any structure. The specification does not support the broad scope of Claims 1-11 and 13-17 because the specification does not establish: (A) the structure of any enzyme that can be used in the recited method: (B) regions of the protein structure which may be modified without affecting the cleavage activity; (C) the general tolerance of the cleavage activity to modification and extent of such tolerance; (D) the structure of all motifs that can be cleaved by any granzyme B; (E) regions of the motif structure which may be modified without affecting the ability to be cleaved; (F) the general tolerance of the cleavage motif to modification and extent of such tolerance; (G) a rational and predictable scheme for modifying any residues of a granzyme B or cleavage motif with an expectation of obtaining the desired biological function; and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including using any protein having any structure to cleave a fusion protein having any granzyme B cleavage motif. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

**Written Description**

Claims 1-11 and 13-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to methods using a genus of protein molecules, having any structure, wherein the protein cleaves any granzyme B cleavage motif. The specification teaches only two representative species of such methods, wherein autocatalytic cleavage by a granzyme B-containing fusion protein occurs (Example 3). The specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a means to cleave a fusion protein having a granzyme B cleavage motif. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 4 and 5 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. These claims are directed to methods for cleaving a genus of fusion proteins comprising a granzyme B cleavage motif, P4 P3 P2 P1 $^{\vee}$ P1' P2' P3' P4', wherein residues P1' and P2' (Claim 4) or P3' and P4' (Claim 5) are part of the polypeptide of interest. The specification teaches the structure of no representative species of such methods. Moreover, the specification fails to describe any representative species by any identifying

characteristics or properties other than the functionality of being a means to cleave a fusion protein having a granzyme B cleavage motif, wherein residues P1' and P2' or P3' and P4' are part of the polypeptide of interest. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 9-11, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsen et al, 2000 in view of Harris et al, 1998 (IDS) and further in view of Pharmacia, Inc, 1986. Johnsen et al teach a method of generating an authentic protein of interest. In said method, authentic streptokinase is generated from a fusion protein comprising from the N-terminus, a His6 tag, a factor Xa cleavage motif, and streptokinase. Said fusion protein is cleaved with immobilized factor Xa (pg 6441, parg 5; pg 6442, parg 1). Although Johnsen et al do not specifically teach how they immobilized factor Xa, it is well known in the art that proteins can be immobilized via the N-terminus, the C-terminus, or lysine residues (Pharmacia, Inc). Johnsen et al, 2000 do not teach a method of generating streptokinase by contacting a fusion protein comprising a granzyme B cleavage motif with granzyme B. Harris et al teach that the motif IEAD is a cleavage site for granzyme B (Fig 5A&D). It would have been obvious to a

person of ordinary skill in the art to incorporate the teachings of Harris et al into the method of Johnsen et al, wherein the Xa cleavage motif in the fusion protein of Johnsen et al would be replaced with the IEAD sequence and the fusion protein processed with granzyme B. Motivation to do so derives from the fact that cleavage with granzyme B would generate authentic protein. The expectation of success is high, as methods for making and cleaving fusion proteins were well-known in the art. Therefore, Claims 1-3, 6, 9-11, and 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnsen et al, 2000 in view of Harris et al, 1998 and further in view of Pharmacia, Inc, 1986.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Johnsen et al, 2000 and Harris et al, 1998 in view of Parenti et al, 1993. The combination of Johnsen et al and Harris et al is described above. Said combination does not teach contacting a fusion protein with granzyme B, wherein the fusion protein further comprises a glycine residue in the P2' position of the cleavage motif and said glycine residue is part of the authentic protein. Parenti et al teach a G-protein α-subunit, wherein said α-subunit has a $Gly^2$ residue. It would have been obvious to a person of ordinary skill in the art to adapt the method rendered obvious by the combination of Johnsen et al and Harris et al to make a fusion protein comprising the G-protein α-subunit of Parenti et al and then cleave the fusion protein with granzyme B in order to produce the authentic protein. Motivation to do so derives from the desire to produce the authentic protein for uses such and biochemical assays and generation of antibodies. The expectation of success is high, as the making and cleaving fusion proteins were well-known in the art. Therefore, Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Johnsen et al, 2000 and Harris et al, 1998, in view of Parenti et al, 1993.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Johnsen et al, 2000 and Harris et al, 1998 in view of Martin et al, 2000. The combination of Johnsen et al and Harris et al is described above. Said combination does not teach contacting a fusion protein with granzyme B, wherein the cleavage motif comprises a glutamic acid residue in the P4' position and said glutamic acid residue is part of the authentic protein. Martin et al teach a phospholipase C of B. cereus, wherein said phospholipase C has a $Glu^4$ residue. It would have been obvious to a person of ordinary skill in the art to adapt the method rendered obvious by the combination of Johnsen et al and Harris et al to make a fusion protein comprising the phospholipase C of Martin et al and then cleave the fusion protein with granzyme B in order to produce the authentic protein. Motivation to do so derives from the desire to produce the authentic protein for uses such and biochemical assays and generation of antibodies. The expectation of success is high, as the making and cleaving fusion proteins were well-known in the art. Therefore, Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Johnsen et al, 2000 and Harris et al, 1998 in view of Martin et al, 2000.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boyer et al, 1992 in view of Harris et al, 1998. Boyer et al teach a method of generating interferon by treating a fusion protein comprising a factor Xa cleavage motif and interferon with Xa (Fig 3). Boyer et al do not teach a method of generating interferon by contacting a fusion protein comprising a granzyme B cleavage motif with granzyme B. Harris et al teach that the motif IEAD is a cleavage site for granzyme B (Fig 5A&D). It would have been obvious to a person of ordinary skill in the art to incorporate the teachings of Harris et al into the method of Boyer et al wherein the Xa cleavage motif in the fusion protein of Boyer et al would be replaced with the IEAD

sequence and the fusion protein processed with granzyme B. Motivation to do so derives from the fact that cleavage with granzyme B would generate authentic interferon. The expectation of success is high, as methods for making and cleaving fusion proteins were well-known in the art. Therefore, Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boyer et al, 1992 in view of Harris et al, 1998.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Medabalimi, 2000 in view of Harris et al, 1998. Medabalimi teaches a method of making an authentic protein using a fusion protein that auto-catalytically cleaves, generating the authentic protein (Fig 5). Medabalimi does not teach a method of making an authentic granzyme B using a fusion protein that comprises granzyme B and a cleavage motif therefore, wherein the fusion protein autocatalytically cleaves, generating granzyme B. Harris et al teach a fusion protein comprising granzyme B and a Kex2 cleavage motif as well as the granzyme B cleavage motif IEAD. It would have been obvious to a person of ordinary skill in the art to combine the teachings of Medabalimi and Harris et al to make a fusion protein wherein the granzyme B cleavage motif IEAD is N-terminally adjacent to granzyme B. Motivation to do so derives from the advantage of auto-cleavage, either during expression or after purification, to generate authentic granzyme B. The expectation of success is high, as methods of making auto-cleaving fusion proteins were known in the art. Therefore, Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Medabalimi, 2000 in view of Harris et al, 1998.

Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Johnsen et al, 2000 and Harris et al, 1998 in view of Braun et al, 1999. The combination of Johnsen et al and Harris et al and is described above. Said combination does not

teach contacting the fusion protein with granzyme B in the presence of $Ni^{2+}$ and NTA. Braun et al teach cleaving a fusion protein with factor Xa in the presence of $Ni^{2+}$ and NTA, wherein the concentration of $Ni^{2+}$ and NTA is ~1-10 mM** (pg 32, parg 6). It would have been obvious to a person of ordinary skill in the art to adapt the method rendered obvious by the combination of Johnsen et al and Harris et al such that the fusion protein is cleaved by granzyme B in the presence of $Ni^{2+}$ and NTA, as taught by Braun et al. Motivation to do so derives from the desire to cleave the fusion protein while still bound to the affinity resin. The expectation of success is high, as cleavage of fusion proteins bound to affinity resin was well-known in the art. Therefore, Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Johnsen et al, 2000 and Harris et al, 1998 in view of Braun et al, 1999.

**Baun et al used $Ni^{2+}$/NTA resin from Qaigen, which has a binding capacity of 1000 nmol/ml, i.e., 1 mM (see enclosed product information). More likely than not, not all binding sites of the $Ni^{2+}$/NTA resin are occupied, therefore, the concentration of $Ni^{2+}$/NTA is ~1-10mM.

***Allowable Subject Matter***

No claims are allowable.

**Final Comments**

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
Art Unit 1652